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☐	L6	L5 and (raf or serine or tyrosine or cad or ca or pyk2 or pky2)	80
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☐	L10	L9 or l8	12

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0357762

SCREENING ASSAYS FOR COMPOUNDS

EPREUVES DE SELECTION DE COMPOSES

Patent Applicant/Assignee:
SUGEN INC
Inventor(s):
ULLRICH Axel,
APP Harald,
HIRTH Klaus P,
TSAI Jianming,

Patent and Priority Information (Country, Number, Date):
Patent: WO 9640276 A1 **19961219**
Application: WO 96US8332 19960603 (PCT/WO US9608332)
Priority Application: US 95156 19950607
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AL AM AU AZ BB BG BR BY CA CN CZ EE FI GE HU IL IS JP KG KP KR KZ LK LR
LS LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA UZ VN KE
LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR
IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 12560

Patent Applicant/Assignee:
SUGEN INC...
Patent and Priority Information (Country, Number, Date):
Patent: ... **19961219**
Fulltext Availability:
Detailed Description
Claims
Publication Year: **1996**

Detailed Description

... tissue culture supernatant) whose effect on the phosphorylation of/by the tyrosine kinases or the **dephosphorylation** by the tyrosine 35 phosphatases of a target cell is determined by the assay of...involved in signal transduction. The 30 assays of the invention involve monitoring the phosphorylation or **dephosphorylation** of tyrosine residues on selected substrates involved in signal transduction in a target cell and...to which the test substance was not added. A similar procedure is used to assess **autodephosphorylation** by phosphotyrosine phosphatases.

A further aspect of this embodiment of the invention allows the user...of the test substance on the phosphatase activity is reflected by 30 the degree of **dephosphorylation** detected in the samples treated with the test substance as compared to untreated controls. The...which recognizes the extracellular domain of human IR, and was purified by the Enzymology Laboratory, **Sugen** Inc.

3. PBS (Gibco) : KH2PO4 0.20 g/l, K2HPO4 2.16 g11f KC1 5...

...1, pH7

4. Rabbit polyclonal antiphosphotyrosine antibody (anti-pTyr) was prepared by the Enzymology Laboratory, **Sugen** , Inc.

5. Goat anti-rabbit IgG POD conjugate (Tago, 10 Burlingame, CA, Cat.No. 6430...with the test substance for varying periods of time. The kinetics of the inhibition of **dephosphorylation** by the test substance at

various dosage may thus be obtained
The above results demonstrated that the assay is capable of identifying and evaluating test substances that inhibit **dephosphorylation** of phosphorylated tyrosine residues on the insulin receptor.

This assay may also be used for assessing any test substances for their ability to inhibit the **dephosphorylation** of other substrate molecules, such as insulin-like growth factor 1 receptor (IGF-1R) and epidermal growth factor receptor (EGFR). When assaying the effects of test substances on the **dephosphorylation** of IGF-1R, NIH3T3/IGF-1R cells expressing IGF-IR starved in serum free media...

...antibodies. 'For assaying the effects on EGFR
- 32
on a PA
SUMMM MET (RULE rAUj
dephosphorylation , NIH3T3/EGFR cells expressing EGFR grown in media containing 0-50i for 40 hours were...the effects of test substances on the phosphatase activity of PTP 1B as measured by **dephosphorylation** of EGFR. The assay protocol used is substantially the same as that described in Section...

Claim
... a substrate of interest; and
(b) a detection molecule that can detect the phosphorylation or **dephosphorylation** of the substrate of interest.

23 The kit of Claim 22 further comprising a protein...

1/3,KWIC/2
DIALOG(R)File 349:PCT FULLTEXT

00357601
METHOD AND COMPOSITIONS FOR INHIBITION OF ADAPTOR PROTEIN/TYROSINE KINASE INTERACTIONS
METHODES ET COMPOSES PERMETTANT L'INHIBITION DES INTERACTIONS PROTEINE ADAPTATRICE/TYROSINE KINASE
Patent Applicant/Assignee:
SUGEN INC
Inventor(s):
TANG Peng Cho,
MCMAHON Gerald,
HARRIS G Davis,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9640115 A1 **19961219**
Application: WO 96US8741 19960605 (PCT/WO US9608741)
Priority Application: US 95136 19950607
Designated States:
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AL AM AU AZ BB BG BR BY CA CN CZ EE FI GE HU IL IS JP KG KP KR KZ LK LR
LS LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA UZ VN KE
LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR
IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 17141

Patent Applicant/Assignee:
SUGEN INC...
Patent and Priority Information (Country, Number, Date):
Patent: ... **19961219**
Fulltext Availability:

Detailed Description
Publication Year: **1996**

Detailed Description
... Exp. Biol. 44:241-25S), is the reversible
phosphorylation of certain proteins. The phosphorylation or
dephosphorylation of amino acid residues triggers
conformational changes in regulated proteins that alter their
5biological properties...

...upon by a ligand-bound receptor.

Phosphorylation is a dynamic process involving competing
phosphorylation and **dephosphorylation** reactions, and the
level of phosphorylation at any given instant reflects the
25 relative activities...

1/3,KWIC/3
DIALOG(R)File 349:PCT FULLTEXT
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00357599
PHOSPHATASE INHIBITORS
INHIBITEURS DE LA PHOSPHATASE
Patent Applicant/Assignee:
SUGEN INC
Inventor(s):
MCMAHON Gerald,
HIRTH Klaus P,
TANG Peng Cho,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9640113 A2 **19961219**
Application: WO 96US9960 19960607 (PCT/WO US9609960)
Priority Application: US 95137 19950607
Designated States:
(Protection type is "patent" unless otherwise stated - for applications
prior to 2004)
AL AM AU AZ BB BG BR BY CA CN CZ EE FI GE HU IL IS JP KG KP KR KZ LK LR
LS LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA UZ VN KE
LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR
IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 14624

Patent Applicant/Assignee:
SUGEN INC...
Patent and Priority Information (Country, Number, Date):
Patent: ... **19961219**
Fulltext Availability:
Detailed Description
Claims
Publication Year: **1996**

Detailed Description
... activity of protein tyrosine
phosphatases (PTPs), The compounds of the invention can
30 inhibit the **dephosphorylation** of phosphotyrosine residues of
a substrate wherein the ...neurological disorders,
The compounds of the present invention inhibit
phosphatase activity in cells, so that **dephosphorylation** of
10 various tyrosine kinases, or other phosphatase substrates
involved in the signaling pathway is...for modulating or triggering
signal transduction,
15 The compounds of the invention can inhibit the
dephosphorylation of phosphotyrosine residues of a substrate
wherein the substrate relays signals in a signaling pathway...on the cell

surface, and the signal is relayed
and propagated by the phosphorylation or **dephosphorylation** of
specific tyrosine residues on various substrates inside the
35 cell, The specific interactions between...acts negatively toward
signaling, one
5mechanism by which PTPs normally downregulate signal
transduction involves the **dephosphorylation** of specific
phosphotyrosine residues (pTyr) on PTKs and their substrates
since many PTKs require phosphorylation...

...the
10 signaling pathway, The compounds of the invention can be
used to prevent the **dephosphorylation** of pTyr residues on
receptors or their subunits which normally becomes
phosphorylated upon ligand binding...

...PTK phosphorylation, The compounds of
15 the invention can also be used to prevent the
dephosphorylation of PTKs in which the tyrosine residues
become autophosphorylated or transphosphorylated due to its
basal...

...be used
to enhance or sustain insulin receptor signal transduction by
25 inhibiting the constitutive **dephosphorylation** of the pTyr
sites on the activated insulin receptor. This would allow
the insulin receptor...

...Another mechanism by which PTPs may exert a negative
effect on signaling is through the **dephosphorylation** of
specific pTyr sites to which SH2-containing molecules bind
- 13
SUBSTMUTE SHEET (RULE 26...

...of the
invention can be used to upregulate or prolong signal
transduction by preventing the **dephosphorylation** of pTyr
sites on substrate proteins that normally serve as binding
sites for SH2-containing...embodiment of the invention, the compounds of
the
invention may be used to prevent the **dephosphorylation** of
specific pTyr residues on any substrate, which pTyr residues
are essential to the relay...

...the signal,
Furthermore, the compounds of the invention may be used to
15 prevent the **dephosphorylation** of specific pTyr residues on
any substrate, which pTyr residues are inhibitory to signal
transduction...

...family
25 PTKs have an inhibitory site of phosphorylation in their
carboxy termini which by **dephosphorylation** activates the
kinase activity, Thus, the compounds of the invention can be
used to prevent the **dephosphorylation** of the inhibitory pTyr
in the carboxy termini of kinases which function normally to
30...assessing the inhibitory activity of a
phosphotyrosyl mimetic.

In addition to measuring phosphorylation or
30 **dephosphorylation** of substrate proteins, activation or
modulation of second messenger production, changes in
cellular ion levels...Receptor
In this example, the ability of the compounds of the
35 invention to inhibit **dephosphorylation** of phosphotyrosine
(pTyr) residues on insulin receptor (IR) is described. The
- 46

SUBSTITUTE SHEET (RULE...
...25 recognizes the extracellular domain of human IR, and was purified by the Enzymology Laboratories, **Sugen** Inc.

3, PBS (Gibco): KH2PO4 0*20 g/lF K2HPO4 2,16 g/lF KC1...

...2,
4, Rabbit polyclonal antiphosphotyrosine antibody
30 (anti-pTyr) was prepared by the Enzymology Laboratories,
Sugen , Inc,
5, Goat anti-rabbit IgG POD conjugate (Tago,
Burlingame, CA, Cat,No, 6430) was...dose of
compound 10 from 15,6AM to 250gM, The kinetics of the
inhibition of **dephosphorylation** by compound 10 at low dosage
is similar to that of 10mM vanadate,
The above...

...also be used for testing compounds of the
invention for their ability to inhibit the **dephosphorylation**
of other substrate molecules, such as insulin-like growth
30 factor 1 receptor (IGF-1R) and epidermal growth factor
receptor (EGFR), When assaying the effects of the compounds
on the **dephosphorylation** of IGF-1R, NIH3T3/IGF-1R cells
expressing IGF-1R starved in serum free media...TrkA Receptor
This example describes the ability of the compounds of
the invention to inhibit **dephosphorylation** of phosphotyrosine
(pTyr) residues on an HA-tagged TrkA receptor (TrkA-HA)
overexpressed in PC12...

...Phosphate
Buffered Saline), (Gibco Cat # 14190-029)
6, Viral suspension, Ad5SV40-rTrkA-HA. (Neurobiology
Lab., **Sugen** Inc., -200C. Current stock titer is 4 10' pfu
(plaque forming units)),
is 7. Capture...

Claim
... negatively charged moiety that
binds a divalent metal ion
so that the compound inhibits the **dephosphorylation** of
10 phosphotyrosine residues of a cellular substrate involved in
signal transduction,

2 The compound...

1/3,KWIC/4
DIALOG(R)File 349:PCT FULLTEXT

00357595
METHODS OF INHIBITING PHOSPHATASE ACTIVITY AND TREATMENT OF DISORDERS ASSOCIATED THEREWITH USING NAPHTHOPYRONES AND DERIVATIVES THEREOF
PROCEDES D'INHIBITION DE L'ACTIVITE DE PHOSPHATASE, ET DE TRAITEMENT DE PATHOLOGIES ASSOCIEES A L'AIDE DE NAPHTOPYRONES ET DE LEURS DERIVES
Patent Applicant/Assignee:
SUGEN INC
Inventor(s):
TANG Peng Cho,
MCMAHON Gerald,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9640109 A1 **19961219**
Application: WO 96US8249 19960603 (PCT/WO US9608249)
Priority Application: US 95481955 19950607
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)

AL AM AU AZ BB BG BR BY CA CN CZ EE FI GE HU IL IS JP KG KP KR KZ LK LR
LS LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA UZ VN KE
LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR
IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 13541

Patent Applicant/Assignee:
SUGEN INC...
Patent and Priority Information (Country, Number, Date):
Patent: ... **19961219**
Fulltext Availability:
Detailed Description
Publication Year: **1996**

Detailed Description
... the cell surface, and the signal is
transduced and propagated by the phosphorylation or
dephosphorylation of specific tyrosine residues on various
substrates inside the cell. The specific interactions
between the...negatively toward signaling. one
mechanism by which PTPs normally downregulate signal
transduction involves the **dephosphorylation** of specific
phosphotyrosine residues (pTyr) on PTKs and their substrates
since many PTKs require phosphorylation...

...in the
signaling pathway. The compounds of the invention can be
used to prevent the **dephosphorylation** of pTyr residues on
rece-.-.ors or their subunits which normally becomes
5phcsphorylated upon ligand...
...of PTK phosphorylation. The compounds of
the invention can also be used to prevent the
dephosphorylation of PTKs in which the tyrosine residues
become autophosphorylated or transphosphorylated due to its
10...

...a
method of triggering, enhancing or sustaining insulin
receptor signal transduction by inhibiting the constitutive
dephosphorylation of the pTyr sites on the activated insulin
receptor. This would allow the insulin receptor...Another mechanism by
which PTPs may exert a negative
effect on signaling is through the **dephosphorylation** of
specific pTyr sites to which SH2-containing molecules bind
during signaling. The absence...

...the
invention can be used to upregulate or prolong signal
transduction by preventing the **dephosphorylation** of pTyr
sites on substrate proteins that normally serve as binding
- 10 sites for SH2...
...embodiment of the invention, the compounds of the
invention may be used to prevent the **dephosphorylation** of
specific pTyr residues on any substrate, which pTyr residues
5are essential to the transmissions...

...of the
signal. Furthermore, the compounds of the invention may be
used to prevent the **dephosphorylation** of specific pTyr
residues on any substrate, which pTyr residues are inhibitory
to signal transduction...

...Src family
PTKs have an inhibitory site of phosphorylation in their
carboxy termini which by **dephosphorylation** activates the
kinase activity. Thus the compounds of the invention can be

20 used to prevent the **dephosphorylation** of the inhibitory pTyr in the carboxy termini of kinases which function normally to promote...assessing the inhibitory activity of a phosphotyrosyl mimetic.

In addition to measuring phosphorylation or 15 **dephosphorylation** of substrate proteins, activation or modulation of second messenger production, changes in cellular ion levels...Inununosorbent Assay In this example, the ability of the compounds of the invention to inhibit **dephosphorylation** of phosphotyrosine (pTyr) residues on insulin receptor (IR) is described. The - 41 assay may be...25 recognizes the extracellular domain of human IR and was purified by the Enzymology Laboratories, **Sugen** Inc.

3. PBS (Gibco): KH2PO4 0.20 g/l, K2HPO4 2.16 g/l, KC1...

...pH7

4. Rabbit polyclonal antiphosphotyrosine antibody 30 (anti-pTyr) was prepared by the Enzymology Laboratories, **Sugen** , Inc.

5. Goat anti-rabbit IgG POD conjugate (Tago, Burlingame, CA, Cat.No. 6430) was...is 15 dependent on the dose of the compound. The kinetics of the inhibition of **dephosphorylation** by the compound is compared to that of vanadate. The assay may also be used for testing compounds of the invention for their ability to inhibit the **dephosphorylation** 20 of other substrate molecules, such as insulin-like growth factor 1 receptor (IGF-1R) and epidermal growth factor receptor (EGFR) . When assaying the effects of the compounds on the **dephosphorylation** of IGF-IR, NIH3T3/IGF-1R cells expressing IGF-1R starved in serum free media...

?logoff hold

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